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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,960	08/03/2001	Michael W. Leviten	R-441	9830

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/922,960	Applicant(s) LEVITEN, MICHAEL W.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-4,13-16 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-12 and 17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Election/Restrictions

Applicant's election with traverse of Invention II, claims 5-10 and 17-24 in paper No. 13, dated 02/20/2003 is acknowledged. It has been determined that it would not require undue burden on the part of the examiner to examine Groups II and III together. While the restriction on the basis that the claimed inventions are patentably distinct is still held proper, Groups II and III have been rejoined in this action.

The traversal is partially on the ground(s) that a search of Invention I claims and Invention II-IV or V claims together would not be an undue burden because a reasonable search would produce results related to the targeting construct of Invention I and the cells and animals of Invention II or methods of using the animals of Invention III or the methods of screening using cells in vitro of Invention IV, or agent of Invention V. This argument is not found persuasive because it is maintained that each of the inventions of Invention I and each of Inventions II-V require a separate search status on the basis of each of Inventions II-V requiring a materially different product from that of Invention I, which is separately classified. In particular, Invention I is directed to methods of making a gene targeting construct that is not necessary to disrupt the ubiquitin ligase E3 in cells or in animals. Materially different constructs can be used to disrupt the ubiquitin ligase E3 gene. Furthermore, the nucleic acid sequences of Invention I and the cells and animals of Invention II are structurally and functionally different and have different uses. As such, Invention I and Inventions II or Invention III require materially different reagents and technical considerations such that a proper search for both inventions would require an extensive search for materially different methods thereby placing an undue search burden upon the Examiner. Furthermore, the nucleic acid of Invention I and the agents of Invention V are structurally and functionally distinct. The nucleic acid is not required for the compounds and the compounds are not necessary for the nucleic acid. The nucleic acid is not necessary for the methods of Inventions III or IV. The cells, the animal and the agents and the methods of using said products have distinct and different purposes from the nucleic acid

construct. Therefore, it is maintained that Invention I and each of Inventions II-V are distinct due to distinct structures, classification and method steps and are thus, separately classified and searched.

The traversal is partially on the ground(s) that a search of the cells or animals of Invention II and the agent of Invention IV together would not be an undue burden because the inventions are related. While the inventions are related, they are patentably distinct. Inventions II and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the cells and transgenic non-human animals of Invention II can be used to determine the role of ubiquitin ligase E3. Furthermore, the product of Invention II can be used in a different manner than in Invention IV and accordingly has been rejoined with Invention III. It would be a burden on the examiner to search more than one method of using the product of Invention II.

The traversal is partially on the ground(s) that a search of the cells or animals of Invention II and the agent of Invention V together would not be an undue burden. The examiner maintains that Invention II and Invention V are patentably distinct. The cells and animals are structurally and functionally distinct from the compounds of Invention V and the cells and animals each have a distinct and different purpose and use from the compounds. The cells or animals can be used for in vitro assays, to study function of glucocorticoid-induced receptor, to produce proteins, or to test gene expression while the compounds can be used to modulate gene product function in vitro. The examiner maintains that Invention II and Invention V are structurally and functionally distinct, have different purpose and use, and are classified differently. Furthermore, the burden required to search the cells or animals with the compounds, which have a different classification, would be undue.

The traversal is partially on the ground(s) that a search of the cells or methods of Invention III and the methods of Invention IV together would not be an undue burden because the inventions are

related. While the inventions are related, they are patentably distinct. The methods of each of Inventions III and IV are materially different and plurally independent from each other because each is practiced with materially different process steps and technical considerations and requires materially distinct protocols and reagents. Invention III uses a transgenic non-human animal. Invention IV uses cells, in vitro. It require an undue burden to search the distinct methods of Inventions III and IV, which are separately classified.

The traversal is partially on the ground(s) that a search of the cells or methods of Invention III and the agents of Invention V together would not be an undue burden because the inventions are related. The inventions are related only in that the agents may modulate the ubiquitin E3 ligase that is deficient from the animals used in the methods of Invention III. A search of Invention III would not necessarily reveal all of the agents encompassed by Invention V. A search of the agents of Invention V would not reveal the method steps of Invention III. Furthermore, Inventions III and V are patentably distinct because the methods of Invention III can be used to identify modulators of ubiquitin ligase E3 expression or activity in vivo while the agents of Invention V can be used to modulate ubiquitin ligase E3 expression or activity in cells. The methods are not necessary to make the agent. The burden required to search Invention III and V together would be undue.

The traversal is partially on the ground(s) that a search of the cells or methods of Invention IV and the agents of Invention V together would not be an undue burden because the inventions are related. The inventions are related only in that the agents may modulate the ubiquitin E3 ligase that is deficient from the cells used in the methods of Invention IV. A search of Invention IV would not necessarily reveal all of the agents encompassed by Invention V. A search of the agents of Inventions V would not reveal the method steps of Invention IV. Furthermore, Inventions IV and V are patentably distinct the methods of Invention IV can be used to identify modulators of ubiquitin ligase E3 expression or activity in vitro

while the agents of Invention V can be used to treat disease symptoms in vivo. The methods are not necessary to make the agent. The burden required to search Invention IV and V together would be undue.

With exception of arguments directly pertaining to Inventions II and III, which have been rejoined, the restriction requirement is still deemed proper and is therefore made **FINAL.**

Claims 1-29 are pending, however, claims 1-4,13-16 and 27-29 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 13. Claims 5-12 and 17-26 are under current examination.

Priority

The specification declares priority to 3 US provisional applications: 60/215,397, filed 06/29/2000 and 60/223,461 filed 08/07/00 and 60/223,385, filed 08/07/00. The oath claims priority to only two applications: 60/223,461 filed 08/07/00 and 60/223,385, filed 08/07/00. Clarification as to which documents applicants intend to claim priority to is necessary. If the oath is defective, a new oath must be filed.

Specification

The disclosure is objected to because the data disclosed in Example 1, *Embryonic Lethality,* is unclear. The text discloses that at a stage where wild type and heterozygous mutant embryos are at embryonic development stage E8.5 having 6-9 formed somites, the homozygous mutants are arrested in development and have no somites formed. However, Table 1 discloses that 3 homozygous mutant embryos from Litter 2 had 6-9 somites. Furthermore, column 6 in Table 1 is unclear as it is not known what the term "unknown" is referring to and whether the '/' is to be interpreted as a mathematical division sign or should be interpreted as the word "or" or "and".

The disclosure is objected to because the data disclosed in Example 1, *Expression,* is unclear. It is not stated what RNA transcripts are being detected or how or if this relates to the gene disruption.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-12 and 17-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, pages 1099-1111 (also available at www.uspto.gov).

Claims are drawn to a cells and transgenic non-human animal comprising a disruption in an ubiquitin ligase E3 gene. Some claims limit the transgenic animal to a mouse. Other claims limit the animal to a mouse comprising a disruption in an ubiquitin ligase E3 gene wherein the mouse exhibits phenotypes associated with embryonic lethality. Claims are also drawn to methods of making and using the transgenic mouse to screen for modulators of an ubiquitin E3 ligase, or modulators of the phenotype of the claimed transgenic mouse.

Claims 5-12 and 17-26 encompass more than one ubiquitin E3 ligase gene as they are drawn to "an ubiquitin E3 ligase gene". The claims encompass any ubiquitin E3 ligase gene that may exist in each and every species of animal. While the specification and the art teaches that are several members of the ubiquitin E3 ligase gene superfamily (page 2, lines 7-15 and Rolfe, 1997, J. Mol. Med., Vol. 75, pages 5-17), the specification teaches only one, mouse ubiquitin E3 ligase gene (SEQ ID NO:1) and its disruption in mouse. Therefore, adequate written description to support the claims of a transgenic animal encompassing more than the one, disclosed ubiquitin E3 ligase gene disruption is lacking.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification provides examples of the methodology to make transgenic mice comprising a disruption in the ubiquitin ligase E3 gene comprising SEQ ID NO:1. In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In the instant case, the claimed invention encompasses transgenic animals comprising a disruption in any ubiquitin ligase E3 gene. The phenotype(s) of the claimed animals cannot be predicted because the art of making transgenic animals or knockout animals is highly unpredictable. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (2000, Comparative Medicine, Vol. 50, pages 12-15) noted:

> "The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has 'no phenotype'."

This clearly indicates that the phenotype of a transgenic mouse or rat or any animal cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In case of a knockout animal, it is not possible to

adequately describe the claimed animals because the effects of inactivating a gene cannot be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650,550) produced a knockout mouse lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see column 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, the result of disrupting any ubiquitin ligase E3 gene in any non-human animal cannot be predicted in the transgenic animals encompassed by the invention. With the limited information disclosed in the specification, an artisan would not have been able to predict whether all these animals would have had same or different phenotypes compared to transgenic mouse comprising a disruption in the ubiquitin ligase E3 gene encoded by SEQ ID NO:1. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 5-12 and 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cell whose genome comprises a disruption in an endogenous ubiquitin ligase E3 gene and a mouse embryo comprising a homozygous disruption in the ubiquitin ligase E3 gene comprising SEQ ID NO:1 wherein said embryo exhibits embryonic lethality, arrested development, or small, abnormal or reabsorbing egg cylinders, does not reasonably provide enablement for any species of transgenic non-human animal with a disruption of any ubiquitin ligase E3 gene wherein said transgenic animal has any phenotype. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 5-7,9 and 24 are directed to cells comprising a disruption in an ubiquitin ligase E3 gene. Claims 8, 10,17-23 are directed a transgenic animal comprising a disruption in an ubiquitin ligase E3 gene (claims 8 and 17-22) and methods of making the animal (claim 10 and 23) wherein the animal is a mouse (claims 10 and 17-23) wherein the mouse exhibits either embryonic lethality (claim 17), developmental arrest (claims 17 and 18), undetectable homozygous offspring after embryonic day E8.5 (claim 19), failure to develop somites (claim 20), reabsorbing egg cylinders (claim 21) or abnormal egg cylinders that resemble E8.5 egg cylinders at embryonic day E.7.5 (claim 22). Claims 11,12,25 and 26 are directed to methods of identifying an agent that modulates an ubiquitin ligase E3 gene or modulates a phenotype associated with disruption of an ubiquitin ligase E3 gene using a mouse comprising a disruption in an ubiquitin ligase E3 gene. Claim 21 is directed to a method of identifying an agent that modulates a condition associated with a disruption in the delta-opioid receptor using a mouse comprising a disruption in the delta-opioid receptor gene.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or

absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Molec. Biol. 7, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997, Molec. Biol. 7, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins (1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the

desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another.

The art at the time of filing also held that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Furthermore, other potential methods of generating transgenic embryos using homologous recombination had not been developed at the time the invention was made (McGreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929;

Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). Thus, at the time of filing, the phenotype of transgenic knockout mice was unpredictable and knockout animals could not be prepared for any species other than mouse.

1) The specification fails to enable making and/or using a non-human transgenic animal comprising a disruption in any ubiquitin ligase E3 gene comprising any phenotype. Claims encompass i) any species of ii) postnatal animal comprising a disruption in iii) any ubiquitin ligase E3 wherein the disruption is either iv) homozygous or heterozygous and wherein the animal has v) any phenotype. As stated above, at the time of filing, the art of making transgenic knockout animals was unpredictable and genes could only be knocked out in mouse. Therefore, one of skill in the art at the time the invention was made would not be able to make and/or use any species of animal comprising a disruption in an ubiquitin ligase E3 gene. The specification further fails to enable making and/or using a postnatal mouse homozygous for a disruption in the ubiquitin ligase E3 gene because the mouse embryos die by embryonic day E8.5. Thus, postnatal mice cannot be obtained. The art at the time of filing also taught a number of ubiquitin ligase E3 genes. While the state of the art was such that more than the disclosed ubiquitin ligase E3 gene comprising SEQ ID NO:1 could be knocked out in mouse, the phenotype of said mouse would be unpredictable. As such, disruption of another mouse ubiquitin ligase E3 gene (itchy) results in a phenotype very different from that of the mouse disclosed in the instant invention (Perry, 1998, Nature Genetics, Vol. 18, pages 143-146). The specification discloses that the phenotype of mice heterozygous for a disruption in an ubiquitin ligase E3 gene comprising SEQ ID NO:1 were indistinguishable from wild type. However, the specification does not disclose how one would use heterozygous mice. Claim 8 encompasses a mouse with a disruption in an ubiquitin ligase E3 gene comprising SEQ ID NO:1 that exhibits any phenotype. However, the specification fails to disclose how one would use this claimed mouse. Therefore, the specification only enables making and using a transgenic mouse embryo comprising a homozygous disruption in the ubiquitin ligase E3 gene

comprising SEQ ID NO:1 wherein the embryo exhibits embryonic lethality, arrested development, or small, abnormal or reabsorbing egg cylinders .

2) The specification fails to enable making transgenic mice using any species or type of cell other than mouse ES cells as encompassed by claim 10.The specification discloses injecting mouse ES cells comprising a disruption in the ubiquitin ligase E3 gene comprising SEQ ID NO:1 into a blastocyst to generate transgenic animals (page 14, lines 25-30). However, the specification and the art at the time of filing fail to disclose any cells other than mouse ES cells that contribute to the germline. Furthermore, no teachings or guidance are offered in regard to how one would have prepared the mice of the instant invention using stem cells from any species other than mouse. Therefore, the guidance offered in the specification is limited to the production of knockout mice using mouse ES cells. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make a transgenic mouse using ES cells from any species other than mouse.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-7 and 9 are drawn to cells comprising a cell comprising a disruption in an ubiquitin ligase E3 gene. It is not clear whether the claims encompass cells within an animal or are meant to encompass isolated cells in culture.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5,6,8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Perry (1998, Nature Genetics, Vol. 18, pages 143-146). Perry taught a mouse comprising a disruption in the *Itch* locus, which encodes an ubiquitin ligase E3 gene. The mice of Perry inherently comprise cells with a disruption in the *Itch* locus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beach (1999, USPN 5,919,997) in view of Perry (1998, Nature Genetics, Vol. 18, pages 143-146).

Beach taught transforming a cell with a nucleic acid construct comprising a disruption in the INK4 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous INK4 locus, and using said cell to generate a knockout mouse whose genome comprises a disruption in the INK4 gene (column 14, lines 61-66). Beach taught administering compounds to the transgenic knockout mice comprising a disruption in the INK4 gene to screen for agents that affect the INK4 mutant phenotype and modulate the expression or function of INK4 (column 26, lines 51-54 and claim 11). Beach differs from the claimed invention in that the targeting construct does not disrupt an ubiquitin ligase E3 gene.

However, at the time the claimed invention was made, Perry taught mice comprising a disruption in an ubiquitin ligase E3 gene. Accordingly, it would have been obvious for one of ordinary skill in the art

at the time the claimed invention was made, to use the mice of Perry to screen for compounds that modulate ubiquitin ligase E3 expression or function by assessing changes in the ubiquitin ligase E3 mutant phenotype as taught by Beach. One of ordinary skill in the art would have been sufficiently motivated to replace the INK4 gene with the ubiquitin ligase E3 gene of Perry, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse and to use the mouse to screen for agents that affects or ameliorates a mutant phenotype or regulates gene expression or function. One of ordinary skill in the art would have been sufficiently motivated to disrupt the ubiquitin ligase E3 gene to screen for modulators of ubiquitin ligase E3 expression or function as a means of identifying drugs that treat the phenotypes associated with loss of ubiquitin ligase E3 function including inflammation and hematopoietic cell growth as described by Perry.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner

DEBORAH J. REYNOLDS
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